Remarks/Arguments

The foregoing amendments to the claims are of a formal nature, and do not add new matter. Claims 124, 129-131 and 135-138 are pending in this application. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 USC §101 and 35 USC §112, 1st paragraph

Claims 124, 129-131 and 135-138 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Further, Claims 124, 129-131 and 135-138 remain rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement.

The Examiner indicates that "the invention does not have utility. The reason is that the significance of the ΔCt was based on the use of normal controls…from human blood and did not take into account controls for aneuploidy of the tumor tissue used… is unable to find either in the specification or in the art, an explanation of how Ct values are calculated, nor what the significance of such are……. It is not clear how measurements of hundredths of PCR cycle can be made, nor what the significance of a difference of 1 or 2 PCR cycles would be. given the paucity of information, the data do not support the implicit conclusion of the specification that PRO290 shows a positive correlation with lung SqCCa or other cancer, much less that the levels of PRO290 would be diagnostic of such." The Examiner cites Sen *et al.*, Hittelman *et al.*, and Jeanfaivre *et al.*, to show that "an increased copy number for PRO290 in lung tumors tested was less likely due to an increase unique to PRO290 DNA, but rather due to a more general phenomenon of polysomy of the DNA in epithelial cancers". Applicants respectfully disagree.

Applicants submit that the results of TaqMan™ PCR, reported in ΔCt units, are disclosed in the passage on page 539, lines 37-39 of the instant specification. as explained therein, One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Applicants showed that the gene encoding for PRO290 was significantly amplified, that is, it showed approximately 1.22-2.07 ΔCt units which corresponds to $2^{1.22}$ -$2^{2.07}$- fold amplification or 2.297 fold to 4.2-fold amplification in five lung tumors and showed

approximately 1.16-1.56 ΔCt units which corresponds to $2^{1.16}$ -$2^{1.56}$- fold amplification or 2.23 fold to 2.95-fold amplification in two colon tumors.

In support of their showing that these gene amplification values are significant, Applicants submit herewith, a Declaration by Dr. Audrey Goddard. Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.297 fold to 4.2-fold amplification in five lung tumors and the 2.23 fold to 2.95-fold amplification for colon cancer would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration. Thus, barring evidence to the contrary, Applicants maintain that the fold amplification disclosed for the PRO290 gene is significant and forms the basis for the utility claimed herein.

It is also well known that gene amplification occurs in most solid tumors, which includes lung and colon cancers, and is generally associated with poor prognosis. Therefore, the PRO290 gene becomes an important diagnostic marker to identify such malignant lung carcinomas, even if the lung or colon malignancy associated with PRO290 molecule is a rare occurrence. Accordingly, the present specification clearly discloses enough evidence that the gene encoding the PRO290 polypeptide is significantly amplified in certain types of lung or colon carcinoma tumors and is therefore, a valuable diagnostic marker for identifying certain types of lung or colon carcinomas.

Regarding the Examiner's rejection based on the Sen *et al.* reference, Applicants respectfully disagree. As Sen *et al.* discloses in the abstract, "lines of evidence now make a compelling case for aneuploidy being a discrete chromosome mutation event that contributes to malignant transformation and progression process"(emphasis added; see page 82, line 4). Sen adds on page 83, "in colorectal tumors, chromosome aneuploidy is a common occurrence"; and

further on page 84, line 5, "(i)n clinical settings, DNA ploidy measurements have revealed that DNA aneuploidy indicates high risk of developing severe premalignant changes in patients with ulcerative colitis, who are known to have an increased risk of developing colorectal cancer" and also on page 84, line 29 "in addition to being implicated in tumorigenesis and correlated with distinct tumor phenotypes, chromosome aneuploidy has been used as a marker of risk assessment and prognosis in several other cancers (emphasis added)." Sen indicates throughout the article, several instances where aneuploidy is associated with many cancers, including, renal tumors, colorectal tumors, esophageal adenocarcinomas, papillary thyroid carcinomas, human breast cancer, cervical intraepithelial neoplasia, myeloid leukemia, etc. Therefore, in fact, Sen *et al.* teaches that it is highly likely that aneuploidy is associated with cancer and thus, supports the Applicants position that PRO260 is a useful diagnostic marker for lung or colon tumors, even if it were shown that PRO260's amplification was due to aneuploidy.

Regarding the Examiner's rejection based on the Hittelman et al. reference, Applicants again respectfully disagree. Hittelman *et al.* studied premalignant lesions and suggests that epithelial tumors develop through a multistep process driven by genetic instability (see abstract). Hittelman *et al.* showed that a subset of the same molecular changes found in associated tumor were also found in premalignant lesions, suggesting that these premalignant lesions might represent precursor lesions for associated tumors, i.e., a manifestation of a multistep tumorigenesis process. (See Hittelman, page 4, last three lines). Applicants therefore submit that, contrary to the Examiner's rejection, the Hittelman *et al.* reference strongly supports the Applicants position that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk (also see Hittelman, abstract, line 4-7). Hittelman *et al.* adds on page 2, fourth paragraph, line 3: "it is important to identify individuals at significantly increased cancer risk who might best benefit from different types of intervention".

Taken together, even if Applicants were to show that the observed PRO290 gene amplification were due to chromosomal aneuploidy, which Applicants do not contend, identifying genetic biomarkers like the PRO290 gene is a very important and useful step, according to Sen *et al.* and Hittelman *et al.*, in identifying individuals at significantly increased cancer risk. Therefore, both Sen and Hittelman support at least one utility for the PRO290 gene, that is, as a genetic biomarker for precancerous cells.

Regarding the Jeanfaivre *et al.* reference, Applicants submit that Jeanfaivre *et al.* examined, as indicated by the title, "prognostic significance of flow cytometry in squamous cell bronchogenic cancer" and further identified parameters useful to "predict survival". For instance, in line 5 of the summary on the first page, Jeanfaivre *et al.* says "DNA content classified as DNA-diploid and DNA-aneuploid is not a prognostic factor for survival" (emphasis added). That is, Jeanfaivre *et al.* address aneuploidy with respect to cancer survival. Nowhere does the reference refer to cancer diagnosis and further, it does not disclose that aneuploidy is not indicative of cancer diagnosis. Hence the Examiner has misrepresented the teachings of Jeanfaivre *et al.*

Therefore, for the reasons discussed above, neither Sen *et al.*, Hittelman *et al.* nor Jeanfaivre *et al.* support the Examiner's rejection that "further research would be required of the skilled artisan to determine whether PRO290 is overexpressed in any cancer". In fact, Sen *et al.* and Hittelman *et al.* support the Applicants position that PRO290 is useful as a diagnostic for cancer or premalignant cancer (if it were shown that the amplification were due to aneuploidy). Testing of aneuploidy is routine in the art and, as one skilled in the art would clearly know, early detection of lung/ colon cancer provides important information in advance about risk assessment, prognosis and therapy for lung or colon cancer and would know how to make and use PRO290 as a diagnostic tool.

Finally, regarding the rejection based on the controls used in the instant Taqman™ assay, Applicants strongly disagree with the rejection. First of all, the specification clearly states that for controls, "tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a **negative control**, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34)." This protocol and the controls used therein are art accepted. Besides, the same gene amplification protocol and controls have been used to identify several other tumor markers for lung, colon, breast cancer etc. in the same application and have been accepted, both, by the art, and the USPTO. Therefore, the credibility of this assay and its controls have already been acknowledged. Applicants have several allowed cases based on this

very same protocol and its controls. The Examiner seems to be applying a heightened utility standard in this instance, the basis of which is legally incorrect.

Applicants further add that they have shown significant DNA amplification; i.e., 2.297 fold to 4.2-fold amplification in five lung tumors and the 2.23 fold to 2.95-fold amplification for two colon cancers in Table 9A, Example 170 of the instant specification. The fact that 5 lung tumors and 2 colon cancers tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO290 gene is amplified in five lung or two colon tumors or in most tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO290 is considered significant is what lends support to its usefulness as a tumor marker.

Thus, Applicants respectfully submit that the Examiner has not established a *prima facie* case for lack of utility based on the above rejections or the cited references. Applicants request reconsideration and that the 35 U.S.C. §101 rejection be withdrawn based on the totality of evidence presented herein.

Further, Applicants respectfully submit that the skilled artisan would not have to perform undue experimentation in order to make or use PRO290 as a tumor marker based on the results of the gene amplification assay for PRO290 and the state of the art in oncology at the time of filing of this application. Thus, Applicants request that the 35 U.S.C. §112, first paragraph enablement rejection also be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Please charge any additional fees, including

any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (**Attorney Docket No.: 39780-2730P1C49**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

(43,626)

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